Clinical review

Kidney stones

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Kidney stones affect up to 5% of the population, with a lifetime risk of passing a kidney stone of about 8-10%.[1] Increased incidence of kidney stones in the industrialised world is associated with improved standards of living and is strongly associated with race or ethnicity and region of residence.[2] A seasonal variation is also seen, with high urinary calcium oxalate saturation in men during summer and in women during early winter.[3] Stones form twice as often in men as women. The peak age in men is 30 years; women have a bimodal age distribution, with peaks at 35 and 55 years. Once a kidney stone forms, the probability that a second stone will form within five to seven years is approximately 50%.[1]

Summary points

Calcium oxalate (alone or in combination) is the most common type of urinary stone

Low urine volume is the most common abnormality and the single most important factor to correct so as to avoid recurrences

Risk of a recurrent stone is about 50% within five to seven years

Diets low in salt (< 50 mmol/day) and animal proteins (< 52 g/day) are helpful in decreasing the frequency of recurrent calcium oxalate stones

Low calcium diets are not recommended to prevent recurrent stones, as they increase urinary oxalate excretion and may result in negative calcium balance

Most ureteral stones under 5 mm pass spontaneously

Sources and search criteria

I searched Medline to identify recent articles (1990-2003) related to the evaluation and management of kidney stones. Key words used included kidney stones, urinary calculi, urolithiasis, urinary tract stones, and nephrolithiasis.

Classification and pathophysiology

Kidney stones are broadly categorised into calcareous (calcium containing) stones, which are radio-opaque, and non-calcareous stones. On the basis of their composition, stones are classified as shown in the table. The figure shows multiple calcium oxalate stones.

Recent evidence indicates that formation of kidney stones is a result of a nanobacterial disease akin to *Helicobacter pylori* infection and peptic ulcer disease.[4] Nanobacteria are small intracellular bacteria that form a calcium phosphate shell (an apatite nucleus) and are present in the central nidus of most (97%) kidney stones and in mineral plaques (Randall's plaques) in the renal papilla. Further crystallisation and growth of stone are influenced by endogenous and dietary factors. Urine volume, solute concentration, and the ratio of stone inhibitors (citrate, pyrophosphate, and urinary glycoproteins) to promoters are the important factors that influence crystal formation. Crystallisation occurs when the concentration of two ions exceeds their saturation point in the solution.

Risk factors for kidney stones

A precise causative factor is not identified in most cases. A family history of kidney stones (increases risk by three times), insulin resistant states, a history of hypertension, primary hyperparathyroidism, a history of gout, chronic metabolic acidosis, and surgical menopause are all associated with increased risk of kidney stones.[5–11] In postmenopausal women, the occurrence of kidney stones is associated with a history of hypertension and a low dietary intake of magnesium and calcium.[12] Incidence of stones is higher in patients with an anatomical abnormality of the urinary tract that may result in urinary stasis (box 1). Most patients (up to 80%) with calcium stones have one or more of the metabolic risk factors shown in box 2, and about 25% of stones are idiopathic in origin. Box 3 shows the various drugs that increase the risk of stone disease.

Hypercalciuria

Hypercalciuria is defined as excretion of urinary calcium exceeding 200 mg in a 24 hour collection or an excess of 4 mg calcium/kg/24 h. Hypercalciuria is the most common metabolic abnormality in patients with calcareous stones and results from various mechanisms.

Absorptive hypercalciuria—Increased absorption of calcium from the gut results in increased circulating calcium, resulting in increased renal filtered load. The

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Box 1: Anatomical abnormalities that increase the risk of stone disease

- Obstruction of the pelviureteral junction
- Hydronephrotic renal pelvis or calices
- Calyceal diverticulum
- Horseshoe kidney
- Ureterocele
- Vesicoureteral reflux
- Ureteral stricture
- Tubular ectasia (medullary sponge kidney)

exact mechanism is unknown but seems to be inherited in an autosomal dominant fashion, and the jejunal mucosa is hyper-responsive to vitamin D. Absorptive hypercalciuria is very common, but most patients remain asymptomatic and do not experience stone formation.

Renal hypercalciuria—Increased excretion of calcium in urine results from impaired renal tubular absorption of calcium. This occurs in about 2% of patients with recurrent stone formation.

Resorptive hypercalciuria—Increased resorption of bone occurs as a result of primary hyperparathyroidism. This occurs in about 5% of patients with recurrent stone formation. The risk of renal stones is increased in primary hyperparathyroidism and returns to baseline about 10 years after parathyroidectomy. Patients who had stones before undergoing parathyroidectomy have a 27 times greater risk of stone formation after parathyroidectomy than do patients without hyperparathyroidism.[8]

Hyperuricosuria

Uric acid is the end product of purine metabolism and is either derived from exogenous (dietary) sources or produced endogenously during cell turnover. Chronic metabolic acidosis can result in protein metabolism and thus increased excretion of urate and formation of kidney stones.[10] Pure uric acid stones are rare but recur frequently. Low urinary pH (pH$<$5.5) is the most common and important factor in uric acid nephrolithiasis; in normouricosuric stone disease the primary defect seems to be in the renal excretion of ammonia and is linked to an insulin resistant state.[6] Hyperuricosuria occurs in 10% of patients with calcium stones, where uric acid crystals form the nidus for deposition of calcium and oxalate. A history of gout doubles the risk of kidney stones in men.[9]

Hyperoxaluria

Hyperoxaluria is defined as urinary excretion of oxalate in excess of 45 mg/day. On the basis of the mechanism, it is classified as follows.

Classification of kidney stones

Composition	Causative factors	Frequency (%)
Calcium oxalate, phosphate, or both	Underlying metabolic abnormality	60-80
	Idiopathic (25%)	
Struvite (triple phosphate)	Infection	10-15
Uric acid*	Hyperuricaemia and hyperuricosuria	5-10
	Idiopathic (50%)	
Cystine	Renal tubular defect	1
Other (xanthine, indigo, triamterene, indinavir*, etc)		1

*Pure uric acid and indinavir stones are radiolucent. Cystine stones are radio-opaque because of the sulphur content.

Enteric hyperoxaluria—This results from increased intestinal absorption due to ileal disease (Crohn's disease, ileal bypass) or short bowel syndrome, low calcium intake, or gastrointestinal decolonisation of *Oxalobacter formigenes*. *Oxalobacter* is an intestinal bacterium that degrades dietary oxalate, and decolonisation of the gut results in increased absorption of oxalate. Oral administration of *Oxalobacter* has been shown to decrease urinary oxalate concentration in animals and humans.[13 14]

Increased ingestion (oxalate gluttons)—Dietary oxalate contributes to about half of the urinary oxalate and is inversely proportional to calcium intake in healthy people without gastrointestinal disease.[15] Spinach, rhubarb, beets, chocolate, nuts, tea, wheat bran, strawberries, and soya foods are known to increase urinary oxalate concentrations.[16] Vitamin C supplementation may increase urinary oxalate excretion and the risk of calcium oxalate crystallisation in patients who form calcium stones.[17] Ingestion of grapefruit juice increases excretion of both oxalate and citrate in urine with no net change in its lithogenicity.[18]

Primary hyperoxaluria—This is an inborn error of metabolism (glycolic aciduria).

In experimental animals, testosterone promotes stone formation by suppressing osteopontin expression in the kidney and increasing urinary oxalate excretion. Oestrogen seems to inhibit stone formation by increasing osteopontin expression in the kidney and decreasing urinary oxalate excretion.[19]

Multiple calcium oxalate stones (0.5 x 0.5 cm) in the collecting system of a kidney (reproduced courtesy of C F Verkoelen, Josephine Nefkens Institute, Netherlands)

Box 2: Metabolic risk factors for calcareous stones

- Hypercalciuria (40-60%)
- Hyperuricosuria (25%)
- Hyperoxaluria
- Hypocitriuria
- Other (vitamin A deficiency, hot climates, immobilisation, urinary tract anomalies)

Box 3: Drugs that may increase the risk of stone disease*

- Decongestants: ephedrine, guaifenesin[w1-2]
- Diuretics: triamterene
- Protease inhibitors: indinavir[w3]
- Anticonvulsants: felbamate,[w4] topiramate, and zonisamide[w5]

*The non-dissolving carrier of osmotically controlled release oral (OROS) drugs may be misdiagnosed as kidney stones on *x* ray[w6]

Hypocitriuria

Hypocitriuria is defined as urinary citrate excretion of <250 mg in 24 hours. Urinary citrate forms a soluble complex with calcium that inhibits the formation and propagation of crystals. It is a common correctable cause of recurrent pure calcium phosphate or brushite stones. Women excrete more citrate and have lower incidence of stone formation than men. Urinary citrate is mainly derived endogenously through the tricarboxylic acid cycle and is excreted by renal tubular cells. Intracellular acidosis, acidic diets (diets rich in animal proteins), and hypokalaemia decrease urinary citrate excretion. Fruits such as oranges and grapefruits are the main exogenous sources of urinary citrate. Hormonal replacement therapy in postmenopausal women results in higher urinary calcium excretion, but it also increases urinary excretion of citrate and leads to net inhibition of crystal precipitation, thereby decreasing the risk of calcium stones.[20]

Struvite (triple phosphate) and cystine stones

Various anatomical abnormalities (box 1) promote urine stasis and increase the risk of stone formation by promoting precipitation of crystals. Urinary infection with urea splitting organisms (*Proteus*, *Klebsiella*, *Serratia*, and *Mycoplasma*) creates alkaline urine that promotes the formation of struvite stones. Urinary saturation with struvite occurs only when supranormal excretion of ammonia and alkaline urine occur together. Alkalaemia suppresses renal ammoniagenesis, but the hydrolysis of urea by bacteria liberates ammonia that alkalises urine.

Cystinuria (cystine stones) is an autosomal recessive trait, with an inborn error in the transport of dicarboxylic acids—cystine, ornithine, lysine, and arginine, commonly known as "COLA." The low solubility of cystine results in its precipitation and stone formation.

Urinary glycoproteins

Various urinary glycoproteins (Tamm-Horsfall proteins, bikunin, nephrocalcin, urinary prothrombin fragment I) are inhibitors of stone formation. Their deficiency may promote stone formation.

Clinical features

Kidney stones may present in different ways (box 4), but the classic presentation is with acute loin to groin colicky pain associated with nausea and vomiting. This, combined with renal angle tenderness and microscopic haematuria, is highly predictive of urinary tract stone disease with a sensitivity of 84% and a specificity of 99%.[21] One third of incidental stones may become symptomatic.[22]

Box 4: Clinical features of urinary tract stones

Urinary tract symptoms

- Pain—classic colicky loin to groin pain or renal pain
- Haematuria, gross or microscopic (occurs in 90%)
- Dysuria and strangury

Systemic symptoms

- Restless patient, often writhing in distress
- Nausea, vomiting, or both (shared innervation of renal capsule and intestines)
- Fever and chills (if associated infection)

Asymptomatic

- Incidental stones (one third may become symptomatic)

Investigations

Some experts recommend detailed evaluation even after passage of a single stone, because of the high rate of recurrence. However, medical evaluation and prophylaxis may not be cost effective in patients who form stones less than once every three years.[23] In addition to detailed history, including family history

Box 5: General measures to prevent recurrent stone formation

- Increase fluid intake to maintain urine output of 2-3 l/day:
  Higher fluid intake is modestly effective in practice, and this effect is often offset by an increase in urine sodium as a result of increased sodium intake[31]
  higher fluid intake alone will not prevent recurrent stones in patients with hypercalciuria
- Decrease intake of animal protein (≤52 g/day)[32]:
  Reduces production of metabolic acids, resulting in a lower level of acid induced calcium excretion; increases excretion of citrate that forms a soluble complex with calcium; and reduces supersaturation with respect to calcium oxalate and limits the excretion of uric acid
  - Restrict salt intake (≤50 mmol/day of sodium chloride)[32]:
    Dietary and urinary sodium is directly correlated with urinary calcium excretion, and lower urinary excretion of sodium reduces urinary calcium excretion
  - Normal calcium intake (≥30 mmol/day)[32]:
    Low calcium diets increase urinary oxalate excretion, which may result in more stone formation and possibly a negative calcium balance
  - Decrease dietary oxalate[16]:
    Reduce the intake of foods rich in oxalate—spinach, rhubarb, chocolate, and nuts
  - Cranberry juice:
    Decreases oxalate and phosphate excretion and increases citrate excretion[33]

of stone disease and past history of stone passage, the basic investigations in a patient who has passed a stone are:

- Urinalysis, including urine pH and urine culture
- Serum electrolytes: calcium, phosphate, bicarbonate, uric acid
- Blood urea nitrogen, serum creatinine (renal function)
- Parathyroid hormone, if elevated serum calcium
- Stone analysis, if possible
- Radiological investigations:
- unenhanced helical computed tomography is the best imaging method to confirm (99% diagnostic accuracy) the diagnosis of a urinary stone in a patient with acute flank pain; it also helps with the measurement of stone density and may guide treatment—stones with density >1000 Housnfield units respond less well to lithotripsy
- plain abdominal film (kidney-ureter-bladder view) is important to assess the radio-opacity of stone, to monitor stone progression, and to guide shock wave lithotripsy.
- In a patient with recurrent stones, in addition to the baseline investigations, a 24 hour urine assessment should be done for urine volume and calcium, oxalate, uric acid, citrate, urine sodium, and creatinine excretion. Urine creatinine is measured to determine the accuracy of urine collection.

Management

Management of a kidney stone depends on its size, location, and composition and the presence of anatomical malformation (box 1) and complications. The presence of a complication (complicated stone)—infection or obstruction—may necessitate immediate intervention, whereas uncomplicated stones can be managed conservatively with adequate fluid intake and analgesia. If a stone does not pass spontaneously then definitive treatment is needed to remove it. The goals of treatment are to control symptoms, render the patient stone free, and prevent recurrence.

Management of acute renal colic

The best resolution of renal (ureteric) colic is by either spontaneous passage or removal of the stone. However, until then, the patient needs pain control and agents that may help the stone to pass. In a recent study, addition to conventional treatment of a calcium channel blocker (nifedipine) to relax ureteral muscles, short term prednisone (for five days) to reduce local oedema through its anti-inflammatory action, antibiotics to prevent and treat urinary tract infection, and paracetamol to raise the pain threshold and reduce the need for narcotics boosted the rate of passage of stones and led to fewer lost work days, emergency room visits, and surgical interventions, with a similar side effect profile.[24] An intranasal spray of antidiuretic desmopressin with or without diclofenac sodium has also been shown to be effective in relieving the pain of renal colic, although experience is limited.[25] Local active warming of the abdomen and lower back (42°C) has recently been shown to be an effective treatment of pain and nausea associated with renal colic.[26]

Box 6: Specific treatments to prevent recurrent stones

Calcareous stones

Normocalciuria

- Oral administration of potassium citrate—increases urine pH and citrate excretion in the urine

Hypercalciuria

- Thiazide diuretics—decrease urinary calcium excretion by augmenting tubular reabsorption of calcium, but do not decrease intestinal absorption in absorptive hypercalciuria; the effect may be attenuated or lost after two or more years of treatment
- Addition of potassium citrate may help to control the diuretic induced hypokalaemia
- If magnesium loss is a concern because of chronic diuretic use, consider potassium magnesium citrate
- Potassium phosphate—may suppress calcitriol synthesis and thereby decrease calcium absorption

Hyperuricaemia or hyperuricosuria

- Allopurinol—to inhibit uric acid synthesis and decrease urinary uric acid excretion
- Potassium citrate should be given in addition to increase urine pH, as uric acid precipitates in acidic urine

Hyperoxaluria

- No specific drugs are available to reduce oxalate excretion in the urine
- Pyridoxine, a cofactor in the alanine-glycoxylate pathway, may reduce production of oxalate by inducing enzyme activity; in an observational study, high intake of vitamin B6 (>40 mg/day) was inversely associated with risk of oxalate stone formation in women
- Calcium supplementation (250-1000 mg four times a day) to control enteric hyperoxaluria; urinary oxalate may decrease, but a concurrent rise in calcium may negate the beneficial effect
- Cholestyramine reduces intestinal absorption of oxalate, but no trials have shown its efficacy in preventing recurrent stones
- Probiotic treatment with *Oxalobacter formigenes* has recently been shown to significantly reduce oxalate excretion in both animals and humans[13 14]; however, trials are pending to show its role in clinical practice

Hypocitriuria

- Potassium citrate—to increase citrate excretion

Struvite stones

- Treatment of infection is mandatory and may be needed in the long term
- Acetohydroxamic acid, a urease inhibitor, has been shown to reduce the urinary saturation of struvite but is associated with high frequency of side effects (deep vein thrombosis, haemolytic anaemia), which limits its use

Cystine stones

- Treatment must include increasing urine output to about 3 l/day and adequate alkalinisation (urine pH>7.0) with potassium citrate
- In addition, specific agents such as α mercaptopropionylglycine or *d*-penicillamine that form soluble complexes with cystine are used

About 90% of ureteric stones smaller than 5 mm pass spontaneously, compared with about 50% of stones between 5 mm and 10 mm, so conservative management is preferred for ureteric stones.[27] Depending on the size of the stone, the average time to pass the stone ranges between one week and three weeks, and the passage of the stone is most accurately assessed by a plain film (kidney-ureter-bladder view) every one to two weeks to monitor progression. An observation period of three to four weeks is reasonable unless urgent intervention is indicated for intractable symptoms, infection, or obstruction.

Additional educational resources

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Auge BK, Preminger GM. Surgical treatment of urolithiasis. *Endocrinol Metab Clin N Am* 2002;31:1065-82

Information for patients

National Institute of Diabetes and Digestive and Kidney Diseases (www.kidney.niddk.nih.gov/kudiseases/topics/stones.asp)—presents simple and concise information about kidney stones

Urology Channel (www.urologychannel.com/kidneystones/index.shtml)—provides a general overview of kidney stones, including the role of naturopathic treatments in prevention of stones

Patient UK (www.patient.co.uk/showdoc.asp?doc = 23068865)—provides simple information on kidney stones

Your Medical Source (yourmedicalsource.com/library/kidneystones/KS_whatis.html)—provides information about diagnosis, management, and prevention of kidney stones

Surgical treatment

Surgical management has recently been reviewed elsewhere.[28] About 10-20% of all kidney stones need radiological or surgical intervention to remove the stone. For proximal ureteric stones, shock wave lithotripsy is useful if the stone is less than 1 cm in size, and ureteroscopy is more successful for stones larger than 1 cm. The preferred approach for distal ureteric stones is controversial. Shock wave lithotripsy and ureteroscopy have shown similar stone-free rates in distal ureteric stones of less than 7 mm. Ureteroscopy is less expensive than shock wave lithotripsy but is more time consuming and technically demanding. Shock wave lithotripsy is less efficacious if the stone is dense (attenuation value of more than 1000 Housnfield units) on helical computed tomography and might adversely affect ovarian function when used for distal ureteric stones in women. Ureteroscopy using the holmium:yttrium-aluminum-garnet (YAG) laser (photothermal lithotripsy) is effective for stones of all compositions and sizes, with a success rate of 97-100%.[29]

Medical treatment to prevent recurrent stones

Medical management to prevent recurrence after a first stone episode is not cost effective.[23] All patients should be advised to follow general treatment recommendations (box 5) for prevention of stone recurrence, and specific treatment (box 6) should be advised to patients with specific problems or with frequent recurrences (a stone at least every three years). Medical prophylaxis is effective in up to 80% of patients with recurrent calcium stones.[30]

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